Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 11 [7] June 2022 : 133-139

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation Development and Evaluation of Orodispersible Tablets of Cilnidipine by Direct Compression Method

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ABSTRACT

Orodispersible tablets (ODT) are those tablets that dissolve or disintegrate quickly in the oral cavity without necessity of water. In the present study orodispersible tablet of Cilnidipine (anti-hypertensive agent) was formulated by direct compression method with a view to increase safety and efficacy of drug molecule as well as to attain better patient compliance. Cilnidipine is an anti-hypertensive drug and it acts as a Calcium channel blocker. The aim of this study was to develop Oro-dispersible tablets of Cilnidipine with increased rate of dissolution using sodium starch glycolate and cross carmellose sodium as a super disintegrants and micro crystalline cellulose as a binder. Mannitol gives better mouth feel effect though it is used as a binder and Sodium saccharine is used as a flavour. The tablets formulated were evaluated for various parameters like thickness, disintegration time, hardness, friability, wetting time and In-vitro dissolution time. All the parameters were evaluated and found within limits. Among developed formulations of Cilnidipine, batch F4 disintegrate within 18.36 seconds. Almost 90% of drug released from all formulations within 18 min. On the basis of least disintegration time, Batch F4 (consisting of 6.66% of Sodium starch glycolate, 5% of Cross carmellose sodium and 25% of Micro crystaline cellulose) is considered as optimized batch for ODT of Cilnidipine.

Keywords: *Orodispersible tablet, direct compression, Cilnidipine, SSG, MCC Etc*

Received 11.03.2022 Revised 27.05.2022 Accepted 19.06.2022

INTRODUCTION

The Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Orodispersible tablets are also known as "Orally disintegrating tablets", "Mouth dissolving tablets", "Melt in mouth", "Fast dissolving drug delivery", "Rapimelts tablets", "Porous tablets", "Quick dissolving tablets" etc. Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia and Centre for Drug Evaluation and Research (CDER).[1]US FDA stated ODT tablets as "A solid dosage form containing medicinal substances which disintegrates fastly within a matter of seconds, when put upon the tongue." European pharmacopoeia also adopted the term "Orodispersible tablet" as a tablet that is to be placed in the mouth where it disperses, quickly before swallowing despite various terminologies used.[2] The active pharmaceutical ingredient (API) released from the ODT may be intended to act locally in the oral cavity or to be absorbed either directly via the oral mucosa (transmucosal absorption) or via the intestinal barrier (intestinal absorption) after swallowing the drug-loaded saliva. The different absorption routes and rates may have an important impact on the pharmacokinetic properties of the product and in consequence, the overall drug development strategy of the pharmaceutical company.

Recent studies shows that patients purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%).[3] Quickly disintegrating / dissolving tablets are one of such examples of safe drug delivery system for patients because of its rapid disintegration or dissolution in mouth with saliva. Advantages of this drug delivery system includes ease of portability, administration without water, accurate dosage forms, rapid onset of action, substitute to liquid dosage forms, absolute for pediatric and geriatric patients.[4]

Objective of this study was to formulate directly compressible orally disintegrating tablets of Clinidipine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration for the treatment of high blood pressure (hypertension)for rapid

dissolution and absorption of drug which may produce rapid onset of action.[5] Clinidipine is a dihydropyridine calcium channel blocker with action on both N- and L-type calcium channels used to treat hypertension.. Cilnidipine acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of norepinephrine and suppressing the increase in stress blood pressure. [6] Clinidipineis rapidly absorbed after oral dose. Peak plasma concentration occurs 2 to 4 hours and its plasma half-life is about is about 3 to 4 hours after an oral dose. It is water insoluble and tasteless. Therefore, it was selected as a model drug for the preparation of mouth dissolving tablets.[7]

MATERIAL AND METHODS

Cilnidipine was purchased from Ajanta Pharma (Paithan). Croscarmellose sodium, microcrystalline cellulose and Sodium starch glycolate was obtained as a gift sample from Lupin Pharmaceuticals (Aurangabad). Methanol was purchased from Molychemlab (Mumbai) Magnesium stearate, Mannitol, Sodium saccharine, Talc and Distilled Water was obtained from Research Lab of MES's College of Pharmacy, Sonai. All other ingredients were of analytical grade.

METHOD:

Characterization of drug and excipients:

Physical Characteristics

In physical characteristics we checked drug physical parameters such as colour, odour and surface nature. Color was checked by visual observation and odor checked by taking a smell of drug.

Melting point

The melting point of the pure Cilnidipine was measured by open tube capillary method.

FT-IR spectral analysis

Cilnidipine and excipients were confirmed by FT-IR spectroscopy. The drug sample and excipients were dispersed in the KBr (200-400 mg) using a mortar, triturating the material into fine powder, and compressing the powder bed into the holder using a compression gauge with 140 mps pressure. spectrum was recorded by putting pellets in the path of the light. The characteristic peaks of the functional groups were interpreted and compared with IR spectrum as given in pharmacopoeial requirements.

Preparation of Cilnidipine ODT by Direct Compression Method

Orodispersible tablets of Cilnidipine were prepared by direct compression method. All the ingredients were passed through the 60- mesh one by one. According to geometrical order the ingredients were mixed after weighing them accuratelyand compacted into tablets of 200mg by employing 6mm round flat punches on 8-station rotary tablet machine(Karnavati mini press-2). A batch of 20 tablets of each formulation was prepared for all the designed formulations.

FORMULATION OF ORODISPERSIBLE TABLETS

All ingredients are in mg.

Table 1: **Formula for 50 tablets.**

Sr. No	Ingredients	R1	R2	R3	R4	R5	R6	R7	R8
1	Cilnidipine	20	20	20	20	20	20	20	20
2	Crosscarmellose sodium	6	12	6	12	12	8	16	20
3	Sodium starch glycolate	6	6	12	12	8	14	14	20
4	Microcrystalline cellulose	30	30	30	30	40	40	40	30
5	Sodium saccharine	4	4	4	4	4	4	4	4
6	Magnesium sterate	2	2	2	2	2	2	2	2
7	Talc	2	2	2	2	2	2	2	2
8	Mannitol	130	130	130	118	112	110	102	102
	Total	200	200	200	200	200	200	200	200

EVALUATION

Pre-compression Parameter

1. Angle of repose(θ) It indicates the flow properties of the powder. The abrasion forces in a loose powder can be measured by the angle of repose. It is explained as maximum angle possible between the surface of the pile of powder and the horizontal plane.

2. Bulk Density

Filling total blend into a graduated cylinder the bulk density was determined. The bulk volume and weight of powder was determined. The bulk density was calculated by using this formula.

$$BD = \frac{\text{Weight of powder}}{\text{Volume of Packaging}}$$

3. Tapped Density

The measuring cylinder containing known amount of blend was tapped for a specified time. The minimum volume occupied in the cylinder and weight of powder blend were measured. The tapped density was calculated by using the formula.

$$TD = \frac{\text{Weight of powder}}{\text{Tapped Volume of Packaging}}$$

4. Carr's Compressibility Index

Carr's Index i.e. compressibility index was determined by using following formula,

$$CI = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \text{x } 100$$

5. Hausner Ratio

Hausner ratio is anfacilityof powder flow. It is calculated by employing the following formula.

$$\text{Hausners Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post -Compression Parameter

1. Weight Variation [8]

20 tablets were selected randomly and weighted separately to determine weight variation.

2. Tablet Hardness

The hardness was calculated by using the Pfizer hardness tester. Hardness of tablet was indicating strength of the tablet. It measures the total force required to break the tablet across tests it. The force is expressed in kg. The hardness of about 3-5 kg/cm^2 is considered to be acceptable for uncoated tablets.[9]

3. Tablet Thickness

Thickness was determined by randomly selecting six tablets from each batch using Vernier caliper. The standard deviation &mean values were calculated [9].

4. Wetting Time

A tissue paper piece (12cmX10.75cm) folded twice was placed in a small Petri dish (ID = 6.5cm) containing 6ml of water. The tablets were put on the paper and the time required for complete wetting was calculated. Three tablets from each formulation randomly selected and the average wetting time was evaluated.[9,10]

5. Water absorption ratio (%)

A tissue paper piece was folded and placed in a petri-dish (Whose Internal Diameter should be 6.5 cm) & contains 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the following equation. [11]

$$R = 100 (W_a - W_b) / Wb$$

Where, W_b was the total weight of the tablet before water absorption.

$W_a$was the weight of the tablet after the water absorption.

6. Friability Test [10]

20 tablets from each batch were examined for friability using Electrolab Fribilator.[9]

Drug content estimation

Randomlyten tablets were selected and average weight of them were calculated. All the tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. Then, the samples were placed in 100 ml volumetric flasks and were diluted with 0.1 N HCL. The mix was shaken frequently and placed for one hour to dissolve drug completely. The mixtures were filtered and proper dilutions were made. The drug content in each tablet was evaluated at lambda max 274 nm against the blank. [11]

7. *In vitro* disintegration time

Disintegration test apparatus as per pharmacopoeia specifications employed for calculating*in-vitro* disintegration time of a tablet. Tablets were placed in six tubes of the basket. Disc was attached to each tube and start the apparatus using 0.1N HCL maintained at 37±2°C as the immersion liquid. The assembly should be increased and lowered between 30 cycles in a minute in the pH 6.8 which is maintained at 37±2°C. The time in seconds taken for complete disintegration. There should be no mass remaining in the apparatus is measured and evaluated. [12-13]

8. *In Vitro* Dissolution Testing

Dissolution study was conducted for all the formulation using USP type-II apparatus (Electrolab, Mumbai, India.). The dissolution test was per-formed using 900ml of 0.1 N HCL was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. 10 ml of aliquots was periodically withdrawn and the sample volume

was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 274 nm.[12] [14]

RESULTS AND DISCUSSION

Characterization of drug and excipients:

Organoleptic characteristics: -

Table 2: Organoleptic properties of drug

Characteristic	Standard as per I.P.	Observed
Color	Yellowish white	Yellowish white
Odor	Odorless	Odorless
Nature	Crystalline	Crystalline powder

The organoleptic properties of Cilnidipine were observed and found to be according to official standards.

Melting point determination:

The melting point of the drug matched with the values found to be 105-109^{0}C.

Solubility:

Solubility of Cilnidipine were determine in various solvent at room temperature calculated by using UV calibration curve in water, 0.1N HCL and in Methanol.

Table 3: Solubility profile of Cilnidipine

Sr. No.	Solvent	Solubility (µg/ml)
1	Water	11.44
2	0.1N HCL	48.62
3	Methanol	94.23

FT-IR of Cilnidipine & Excipients

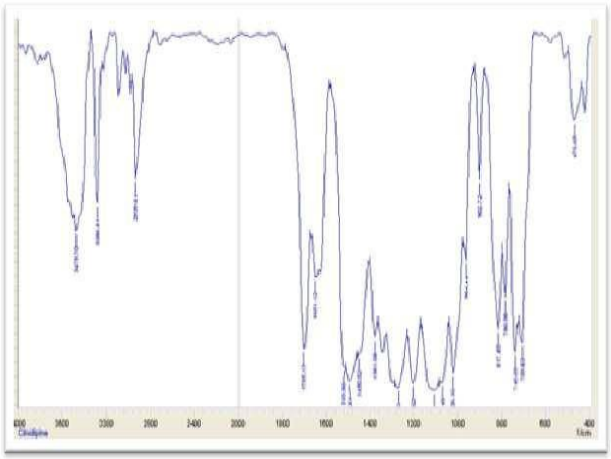

Fig 1: FT-IR spectra of Cilnidipine.

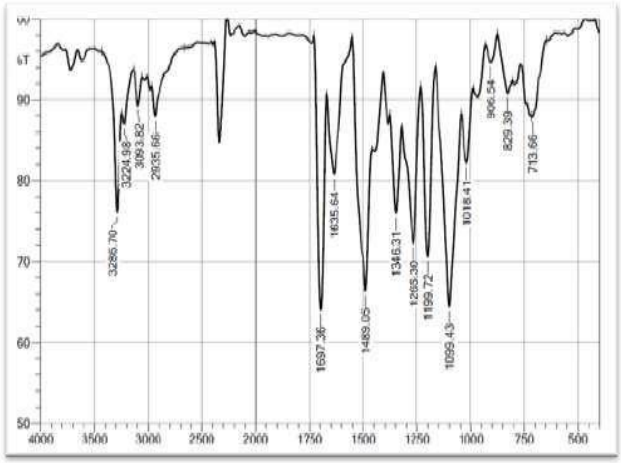

Fig 2: FT-IR of Drug and Excipient mixture

Pure drug Cilnidipine and physical mixture were subjected for IR spectroscopic analysis, to ascertain whether there is no any interaction between the drug and excipient used. The IR spectra obtained was shown in figure. From all the IR spectra it could be concluded that there is neither occurrence of any major extra peak in the formulation compared to the simple spectra of API, SSG and CCS nor any of the major peak is deleted. Slight shifting of peaks in the given range only is considerable. Thus, it could be concluded that all the excipients are compatible with API.

PRECOMPRESSION STUDY:

Evaluation of powder blend:

The characterization of flow properties of powder blends is having vital role in tablet compression. The powder blends with good flow properties gives uniform die fill and consequently it gives the uniform tablet weight.

Prepared powder blend of all batches is evaluated for flow properties and result obtained shown in the table,

Table 4: Evaluation (Pre-compression) parameters of all formulation (R1-R8)

Batch	Bulk density (gm/cm3)	Tap density (gm/cm3)	Carr's Index	Hausner's Ratio	Angle of repose
R1	0.41±0.16	0.46±0.42	11.44	1.19	27.76±0.49
R2	0.44±0.16	0.50±0.74	10.26	1.14	28.40±0.11
R3	0.38±0.40	0.46±0.14	11.29	1.12	27.15±0.36
R4	0.39±0.28	0.49±0.56	12.24	1.17	26.40±0.28
R5	0.42±0.62	0.51±0.53	13.64	1.13	29.84±0.35
R6	0.40±0.52	0.50±0.80	12.00	1.18	27.03±0.12
R7	0.42±0.58	0.51±0.56	15.50	1.16	29.34±0.92
R8	0.41±0.26	0.52±0.64	10.20	1.15	28.34±0.65

Bulk density: The bulk density of powder is important parameter in the compressibility of the powder. 0.38 to 0.44 gm/cm3 was the range reported of bulk density.

Tapped density: The tapped density of powder is important parameters in the compressibility of the powder.

In the range of 0.46 to 0.52 gm/cm3 tapped density was noted.

Car's Index: The Carr's index is indicator of compressibility. It was found to be in the range of 10.26 to 15.50 % indicating good compressibility.

Hausner's ratio: The hausner ratio is another parameter indicating the flow properties. The value of ratio below 1.25 indicates good flow while above 1.25 indicates the poor flow. 1.12 to 1.19 was noted as hausners ratio range & it indicates good flow ablility.

Angle of repose: The angle of repose was noted in the range of 26.40 to 29.84 which indicates good flowability.

POST COMPRESSION EVALUATION:

Table 5. Evaluation (Post-compression) parameters of all formulation (R1-R8)

Batch	Thickness (mm)	Weight Variation ±SD (%)	Wetting Time (Sec±SD)	Hardness (Kg/cm²±SD	DT (Second)	Friability (%)	Drug Content (%)±SD	Water Absorption Ratio (R)±SD
R1	3.39±0.08	3.60±1.80	32±1.09	2.8±0.71	33.21	0.13	96.43±1.02	103.42±0.08
R2	3.41±0.05	4.79±1.75	30±0.81	2.8±0.35	28.12	0.20	98.15±0.54	98.06±0.16
R3	3.42±0.07	3.89±1.90	36±1.03	2.9±1.2	22.51	0.18	97.65±1.07	103.71±0.11
R4	3.34±0.11	3.10±1.20	33±0.902	2.8±0.9	18.36	0.19	95.55±1.35	102.5±0.08
R5	3.45±0.01	3.30±0.70	55±0.975	3.1±1.3	42.92	0.09	94.27±0.45	93.62±0.33
R6	3.52±0.11	2.06±1.05	51±0.885	3.1±1.6	38.61	0.07	96.27±0.46	95.52±0.13
R7	3.39±0.01	3.00±1.0	54±0.851	3,0±0.7	35.74	0.09	98.17±0.74	94.62±0.13
R8	3.44±0.09	3.75±1.05	52±0.994	3.2±1.2	25.30	0.08	96.17±0.33	96.75±0.12

In Vitro Drug Release:

Table 6: % Drug release of all batches

Batch and Time	R1	R2	R3	R4	R5	R6	R7	R8
7	35.91	37.12	36.19	39.41	35.71	36.52	35.69	37.56
14	48.53	49.31	49.48	50.61	47.80	46.12	46.43	47.91
21	58.98	58,43	61.49	60.12	61.32	59.91	59.99	58.62
28	72.18	71.65	73.81	75.44	74.32	74.99	73.53	75.48
35	91.13	90.81	94.19	93.02	88.53	90.17	89.88	92.50
42	92.34	91.58	96.23	94.12	90.71	91.45	90.81	93.68

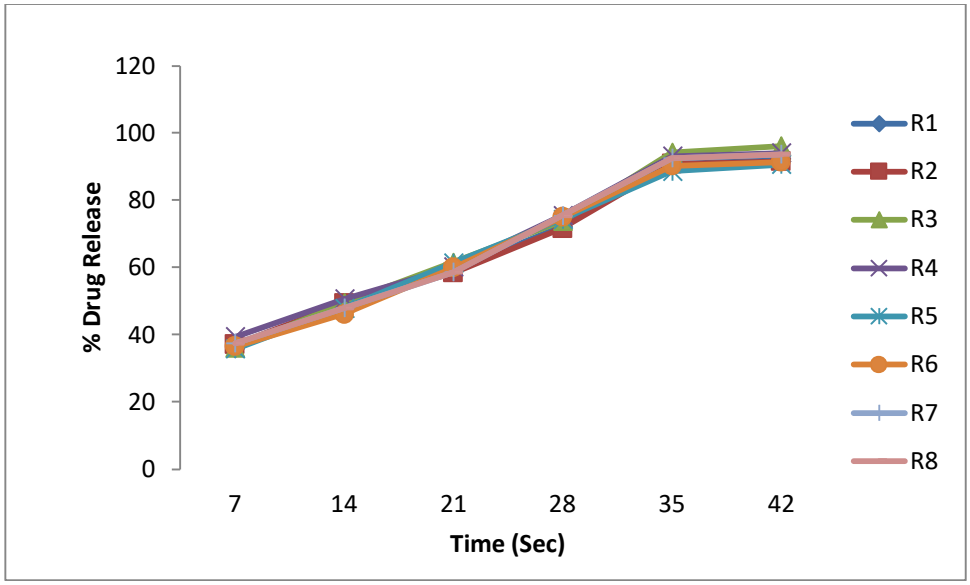

Fig 3: *In vitro* % Cumulative drug release.

- In the range 3.34-3.52 mm thickness of all tablets were observed.
- The average weight of all tablets was found to be within the limits.
- The tablet hardness of tablets found to be within the range i.e., 2.8-3.2 kg/cm2.
- Disintegration time for F5 is maximum i.e., 44.92 sec; while Disintegration time was minimum for F4 i.e.:18.36 sec.
- Percentage Drug Release for tablet formulation F5 is minimum i.e., 90.71% and maximum for F4 i.e., 96.23%

DISCUSSION AND CONCLUSION

The aim of present investigation was to Prepare and evaluate Oro-dispersible Tablet of Cilnidipine. Oral disintegrating tablets (ODTs) of Cilnidipine was successfully prepared by using direct compression method. The availability of assorted technologies and also the manifold benefits of ODTs will surely enhance the patient compliance, rapid onset of action, fast disintegration, low side effect and its popularity in the near future. Combined impact of super-disintegrant SSG and CCS on drug release and disintegration time of tablet was studied. Formulation was optimized using 2^3 full factorial design. The compatibility between Cilnidipine and Excipients were studied by IR analysis. Prepared tablets of all batches were subjected to evaluation parameters like thickness, wetting time, hardness, disintegration time and *in-vitro* dissolution. [12] From the present study it can be concluded that Oro-dispersible tablets of Cilnidipine can be successfully prepared by employing combination of super-disintegrants. Blend of Cilnidipine with excipient established good flow properties and compressibility characteristics. FT-IR studies shows that there were no major interactions occur between Drug and excipients.[15] Among all prepared formulations (F_1- F_8), on the basis of least disintegration time, Batch F_4 (Containing 16 mg of SSG, 16 mg of CCS and 40 mg of MCC) which having DT 18.36 sec and 94.12% drug release at 18 min is better than other formulation. Hence it can be concluded that Oro-dispersible tablet of Cilnidipine can be formulated using super-disintegrant (SSG & CCS). Direct compression method would be an effective perspective in the preparation orodispersible tablets with better results.

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CITATION OF THIS ARTICLE

Suresh Jadhav, Vaibhav Sarang, Shankar Dhobale, Rupali Thorat, Dushyant Gaikwad. Formulation Development and Evaluation of Orodispersible Tablets of Cilnidipine by Direct Compression Method. Bull. Env. Pharmacol. Life Sci., Vol 11[7] June 2022 : 133-139.